

5-1-1936

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THE ETIOLOGY AND CLINICAL DIAGNOSIS
Of
CHOLECYSTITIS AND CHOLELITHIASIS

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Senior Thesis
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April, 1936

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INTRODUCTION

As man's knowledge of anatomy has advanced, so has his skill in the diagnosis of pathological conditions of the body. This was particularly true in relation to morbid processes of the gastro-intestinal tract, for, since the diseased organ could neither be seen or palpated, the diagnosis had to be a symptomatic one. As the medical profession gradually freed itself of the superstitions of the early centuries, and in addition became curious enough to perform post-mortem examinations to find the cause of death, and not simply as an opportunity to do dissection, more accurate conception of intra-abdominal disease processes resulted.

This same insatiable desire has persisted to the present day, and whenever the physician is confronted with a patient who has complaints referable to the intestinal tract, he proceeds to obtain as exact information about that complaint as possible. If it seems at all indicated, the patient is sent to the roentgenologist, in order that the suspected ulcer crater may be seen, to demonstrate the lack of function of the gall bladder by its failure to concentrate, to visualize the kidney stone, or to see the filling defect of the neoplasm. This scientific branch of medicine is a highly necessary one, and should be made available to every patient, but the easy accessibility of its information may be abused. The physician, in many instances is all too liable to allow the roentgenologist to

make the diagnosis, rather than himself. This same tendency is evident also in the temptation to make many laboratory tests, and rely too strongly on the fallible evidence of chemistry, rather than developing his own reasoning and deductive powers.

This paper, therefor, is an effort to present cholecystitis and cholelithiasis and the diagnosis of these related conditions, with disregard to the laboratory and X-ray findings, hoping to encourage the more extensive use of the physician's own tools and aids: his eyes, ears, hands and mind.

The theory has been advanced that cholecystitis and cholelithiasis were unknown to the early Egyptian because of a difference in the diet of those days, yet an Egyptian mummy of about 2000 B. C. has been found, whose gall bladder was packed with stones. (22) The symptom of jaundice associated with abdominal colic is also mentioned by Aristotle in 360 B. C., and since he found constipation with this condition, we may assume that it was due to cholecystitis. Galen in 168 A. D. mentions colic, with nausea and vomiting of bile and constipation. He asserted that jaundice is the result of absorption of bile into the blood; when the body is full of bile he discovered that it was seldom found in the stools. (48, 35) Paulus Aeginetae (53), in his sixth book mentions that jaundice is a diffusion of bile over the whole body. When there is a sense of heaviness in the right hypochondrium it indicates that the ducts are obstructed. If, with this jaundice there is fever and the alvine discharges are white an affection of the gall bladder or its ducts is indicated. For this condition he mentions the use of cholegogue cathartics, such as hellebore. The first mention of gall stones by a European writer seems to be that by Antonius Benivenius who died in 1592. (46) "There was severe excruciating pain in the bowels, the cause of which was not easily understood; this preceded the passing of a stone in the excreta, which made the diagnosis." Apparently the patient died for he mentions taking one hundred twenty stones from the gall bladder of this woman which were various sizes, hard, dark in color, cuboid in shape, and on

breaking them open, showed laminated appearance. He also has described finding a gall stone in the gall bladder, black and the size of a large dry chestnut. (35)

Following the description of the gall stones noted by Antonius Benivenius, Fernelius (35) in 1554 gave a description not only of gall stones but of their associated symptoms. He observed that obstruction of the common duct may lead to a swelling of the gall bladder. A white discoloration of the feces, the passage of dark urine and of jaundice. Ettmüller in his dissertation entitled "De ictero flavo, nigro et albo" (Oper. med., Tom. II, page 1, Colleg. pract., Sect. VII, Cap. IV, page 442) (25 p. 173), gives a remarkably accurate clinical picture of biliary tract disease. He speaks of pain in the precordial region which appears with icterus and is accompanied by nausea, difficult respiration and a reddish color of the urine. He states that fever is often present and in many cases pain in the right hypochondrium, which may either be readily removed or be very difficult to cure, or, lastly, may be removable but shows a tendency to recur. In the latter type, he said, stones were commonly found in the gall bladder. He also noted that colic and icterus are sometimes seen after childbirth and that icterus frequently follows the attack of colic and that it is frequently the result of an obstruction to the flow of bile into the intestine or of insufficient secretion of bile by the liver as is seen from the fact that icterus may occur without an obstruction in the bile passages following fever, the bite of wild animals, abuse of

blood-letting, etc. He observed further that icterus does not necessarily always occur in cases of gall stones. He was convinced that the gall bladder could be extirpated without endangering the life of the animal and he quotes the important experiment of one of the students in Leyden who removed the gall bladder from a dog without observing any bad results. He considered that icterus was due to obstruction of the common bile-duct which caused a regurgitation of bile into the blood. He also states that there is no remedy for gall stones.

The following quotation is probably one of the earliest of the fairly accurate anatomical descriptions of the gall bladder: "Now to speake of the Gal, or the chest of the Gal:-----and it is as a purse or a pannicular vesike in the holownesse of the Lyver, about the middle pericle or lobe, ordeyned to receyve the Cholerike superfluities which are ingendered in the Lyver. The which purse or bagge hath three holes or neckes, by the fyrste he draweth to him from the Lyver the choler, ---- by the second necke he sendeth to the bottom of the stomache choler to further the digestion." (64)

Morgagni in his work "de sedibus et causibus morborum" (25 p. 143), makes an excellent presentation of cholelithiasis. According to him, occlusion of the bile passages is a result of a contraction of the ducts and a thickening of the mucous lining. He observed that if the cystic duct alone is occluded icterus is not observed.

He mentions as predisposing causes, the age of the subject, sedentary habits and other factors.

Haller in his great pathological work "Disputations ad Morborum" presents two cases of post mortem examinations.

(30)

Case 1. This patient had a turgid gall bladder containing many stones. On cutting, it felt like cartilage and contained forty-five stones, but no bile. There was a large stone impacted in the common duct at its junction with the cystic duct. The hepatic pores were double their ordinary capacity. The patient did not have an icterus; was only muddy.

Case 2. A woman aged fifty-two who for six years had had many pains in the right hypochondrium. In the year 1699 after much pain she passed two stones by anus. Examination of this woman showed a gall bladder adherent to the liver and to the duodenum, it having communication with the bladder. "Pain in the right hypochondrium, under the diaphragm, in the area over where the coledochus enters the inferior duodenum; greater and lesser, now graye, now lancinating, continuing indefinitely--these signs are

definitely diagnostic of gall bladder stones." "Nausea and vomiting occur later. The patient becomes jaundiced and the bowels white." He mentions that the prognosis depends on the size of the stone blocking, and this can be told by the state of the jaundice. If it continues to deepen this means complete blockage, fever, delirium and death. (21)

Duprat in 1803 was of the opinion that gall stones were formed during an acute hepatitis, and then block the choledochus, so that there is more pain and general enlargement of the duct system. "-----But only, sometimes, short and fleeting pains, repeated jaundices, etc., these maladies are not yet known because of the state of anatomical research."

Rosenmüller in 1816 (56) was one of the first to venture an opinion as to the function of the gall bladder. He mentioned the fact that the bile flows from the liver to the gall bladder and is condensed and held there until digestion, when it is forced out through the ductus choledochus into the duodenum.

It is interesting to note that Baillie in 1820 (5) was not able to give a much better description of the pathology of the gall bladder than was made 100 to 150 years previously. He found that it was very common, on dissection,

to see adhesions around the gall bladder which, he stated, were a consequence of previous inflammation. He found gall stones very frequently. The gall bladder was sometimes much enlarged with very thick coats and full of stones. If only one stone was found it was usually quite large; he describes one the size of a hen's egg. He found that the composition of the stones varied, very few stones containing bile, and that they were usually laminated with a radiated center. He stated that there was no jaundice if the cystic duct was obstructed, but only inflammation and occasionally suppuration. In discussing the diseases of the gall bladder he states that if the stones stay in the bladder there are seldom any symptoms, but if one of the stones enters the ductus choledochus, excruciating pain results, with languor, sickness and vomiting with jaundice.

Abernethy about the same time (1828) admitted that he was ignorant of the functions of the liver and of the bile. He mentions taking fifteen hundred stones from one gall bladder. Goupil in 1831 (24) describes a syndrome which he calls bilious fever and attributes to hepatitis. This consisted of thirst, anorexia, fever, jaundice and pain in the right hypochondrium.

In 1855 Dickson (20) described icterus associated with gall stones and stated that the symptom of pain is caused by stone passing through the ducts. His description of such an attack does not vary much from that of previous writers. It is that of great pain in the epigastrium soon

extending to the right hypochondrium and associated with nausea, frequent retchings and vomiting.

Niemeyer in 1865 (49) was one of the early pathologists to advance a plausible theory of the formation of gall stones. Briefly, he thought that the calculus was formed around a nucleus of mucous membrane and was the result of too much calcium in the bile, or a decrease in bile acid, thus causing a precipitation of cholesterin and bile pigments. He observed that gall stones occurred more frequently in women than in men and that the greater percentage were cholesterin stones. He also was of the opinion that the pain in the right hypochondrium attributed by so many of the early authors to hypotitis was really the phenomenon of inflammation and ulceration of the gall bladder and bile passages. Coats (13) believed that stones were a result of stagnation of bile from the gall bladder and caused cholecystitis, and Cohnhein (4) in 1890 also thought that stones were caused by stagnation plus some change in the chemistry of the bile, cause unknown. He also believed that inflammation of the gall bladder is caused by stones.

In embryos of 2.5 mm. there is seen a sacculation from the ventral floor of the fore-gut just cranial to the yolkstalk. As this hepatic diverticulum pockets outward, it plunges directly into the splanchnic mesoderm of the ventral-mesentery. Continued growth spreads the mesentery, its mesoderm forming all the connective tissue and smooth muscle associated with the liver and biliary system, the mucosa

being entodermal in origin. The gall bladder and its cystic duct represent a special offshoot of this early diverticulum. Until the sixth or seventh embryonic weeks the gall bladder is solid. (3)

ANATOMY AND PHYSIOLOGY OF THE BILIARY TRACT

The gall bladder is an oblong, pear shaped sac, which is fastened by loose connective tissue in the fossa vesseicae felleae of the liver. When the bladder is full its broad, blind and rounded end projects somewhat beyond the anterior abdominal wall just median from the anterior extremity of the ninth costal cartilage of the right side. From the fundus the body of the bladder extends upward, backward and somewhat to the left and narrowing suddenly goes over at the right side of the porta hepatis into the ductus cysticus. The gall bladder comes into contact below with the transverse colon and behind with the descending portion of the duodenum. The fundus and the posterior inferior surface possess a peritoneal coat. The wall consists of a delicate layer of mostly circular muscle fibres and a mucous membrane from which project numerous ridges, the plicae, arranged in the form of a network. The ductus cysticus leaves the bladder with a marked downward bend, extends downward and to the left and after a short course joins the ductus hepaticus; its mucous membrane presents a series of folds, which are arranged in the form of a spiral,

the spiral valves of Heister, and which correspond to grooves on the external surface. The ductus choledochus runs downward and in the direction of the ductus hepaticus at first in the hepatoduodenal ligament to the right of the portal vein, then in the head of the pancreas at the junction of the left and posterior walls of the descending duodenum, into which it opens near the pancreatic duct or in common with it.

The blood supply is by a small artery, the cystic artery, which is a branch of the right hepatic artery, a derivative of the celiac. The venous drainage is by the cystic vein which opens either into the stem or the right branch of the portal vein.

The nerves of the gall bladder and extra hepatic ducts are derived from the same source as those which go to the liver, arising chiefly in the hepatic plexus. In the circular fibres of the gall bladder the nerves form a plexus similar to Auerbach's plexus in the intestine. Branches from this plexus give rise to a secondary plexus in the mucosa. (59)

The large lymphatic vessels running over the gall bladder bring lymph from the liver and the coats of the gall bladder; they follow the inner side of the cystic duct and end in the mesenteric lymph glands. There is a very dense network of lymph channels in the subserous layer into which enter the sub-mucous sets of lymphatics. There are normally no solitary lymph follicles in the gall bladder similar to those in the appendix. One of the most important

points about the lymphatics of the gall bladder is that they have a very intimate anastomosis with those of the liver. (63)

Kodama (35), by the injection of trypan blue into the subserosa of the first portion of the duodenum, found that the dye passed through the lymphatic vessels along the common duct and entered the wall of the gall bladder. When the solution was injected into the lymphatic vessels immediately beneath the serosa of the gall bladder the dye was carried to the upper part of the duodenum.

Graham has shown that the interlobular lymphatics of the liver connect with the gall bladder and ramify over the head of the pancreas. With injections of Prussian blue into the wall of the gall bladder the dye was seen to pass through the lymphatics into the liver and along the common duct. (25) As the result of studies with experimental cholecystitis in the dog, he has come to the conclusion that infection of the gall bladder can occur through the lymphatics as the result of hepatitis. (54)

The gall bladder has three types of activity, those of absorption, secretion and motor activity. The gall bladder absorbs mainly water so that the hepatic bile, as a result, is concentrated four to ten times. Consequently of this in the fasting human, the gall bladder may contain the entire twenty-four hour output of the liver. The acutely inflamed mucosa does not concentrate or evacuate. However, if the inflammation is patchy or in the muscular or serous

coats the gall bladder will concentrate. If fibrosis occurs as a result of the inflammation, concentration, if any, is light. Cholesterosis does not interfere with concentration or emptying unless it is associated with a moderate or severe cholecystitis. The gall bladder normally secretes a mucoid fluid at a rate of about twenty cc. per 24 hours. One is the rhythmic tonus change which is equal to about 1 to 3 cm. of bile pressure. The other is the tonic contraction of the musculature at a whole and is equal to 20 to 30 cm. of bile pressure. The power of the normal gall bladder is not equal to the secretory pressure of the liver. The chief stimulus of contraction is cholecystokinins which is secreted by the duodenal mucosa. The production of this substance is stimulated mainly by acids and fats in the upper intestine, especially egg yolks and cream. Atropine relaxes the gall bladder but does not abolish the effect of cholecystokinins.

The Sphincter of Oddi. Since the sphincter can resist up to 75 cm. of bile pressure it is obvious that it must relax for the gall bladder to empty itself. Ivy has shown that when the gall bladder contracts, the sphincter relaxes, and states the following findings:

1. Increasing duodenal muscular tone inhibits the flow of bile into the duodenum.
2. Decreasing the duodenal muscular tone increases the flow of the bile into the duodenum.
3. Chemical irritation of the duodenum delays gall bladder evacuation.

4. Atropine favors the flow of bile, pilocarpine stops it.
5. Morphine inhibits the flow of bile.
6. Magnesium sulphate favors the flow of bile.

Ivy has found that there are three types of evacuation of the gall bladder in response to a fat meal:

1. The primary relaxation of the gall bladder with closure of the sphincter, which is only temporary. This condition is rare.
2. Contraction and evacuation start quickly and evacuation occurs rapidly. This type prevails in 95% of the cases.
3. Evacuation starts and then stops, filling of the gall bladder then occurring. This is followed by further evacuation. (32)

Winkelstein (68) Van Meter (31) and Mann (36) believe that the gall bladder is emptied by the pressure of adjacent, distended organs, by the milking action of duodenal peristaltic waves, and by the intra-abdominal pressure of respiration, when the papilla of Vater is open.

Boyd (9) and Mentzer (40) have shown that the cholesterol found in the epithelial cells of the mucosa is due to the absorption and not excretion. The former, in the chemical analysis of a number of gall bladders found that the normal gall bladder showed from 0.51--1.70% cholesterol by weight.

CHOLECYSTITIS

The term cholecystitis is often loosely used to comprise a number of disturbances of the gall bladder, of which some are true inflammations and others perhaps deviations from a normal function or metabolism of the gall bladder. It has been suggested that the term "cholecystopathy" be used instead of the more prevalent cholecystitis. Since the clinical diagnosis of cholecystitis and cholelithiasis is arrived at by a consideration of symptoms and physical findings which could be caused by either of the two conditions this topic will be considered separately.

THE ETIOLOGY OF CHOLECYSTITIS

Incidente. Mentzer (43) in a study of 49,659 new patients at the Mayo Clinic in 1922 found that 5% complained of gall bladder disease and that of 612 necropsy specimens, 62% showed gross lesions of the gall bladder. The Prudential Life Insurance Company found that 33 out of every million died of gall bladder disease in 1919. In 110 women who had been pregnant, 64% showed cholesterosis of the gall bladder and 82% had gall bladder lesions. In 34 patients weighing over 210 pounds 70% showed cholesterosis. Constant (15) in his series of ten thousand of female patients over a period of 5 years found 930 cases of cholecystitis, 60% of which showed calculi. The symptoms of gall bladder disease occur most frequently during the fourth decade or later. Blalock (26) found that 28% of all his cases gave a history of a preceding typhoid infection, the average time between the infection and the appearance of gall bladder symptoms being

five years. The mode of infection of the gall bladder by bacteria, and the type of bacteria found in the gall bladder has been the object of a great deal of experimental work. Bacteriological investigations of the gall bladder have been made in three ways, by cultures of the contained bile or other fluid content, by cultures of the ground up wall of the organ and by the injection of bacteria in experimental animals. Rosenow (57) stressed the desirability of making cultures from the wall rather than from the contents of the organ. His cultures from the wall showed streptococci more frequently than any other type but his most valuable contribution was that the injection of the streptococci into experimental animals produced gall bladder lesions in 79%. In four of the human cases in which he found pure cholesterin stones there were very few bacteria in the wall of the gall bladder and none in the stone. Williams (67) using cultures obtained from macerated gall bladder walls, obtained streptococci in 16% of his 106 cases of cholecystitis and Bacoli in 20%. He found streptococci in 24% and found that these organisms had very slight if any localizing power. Brown (12) found streptococci in 30% (in his series of cases) of the gall bladders studied which had slight lesions and in 75% of the grossly diseased gall bladders. He found that cultures made from tonsillar pus and injected intravenously into rabbits produced no lasting bacteremia, no septicemia and lesions only in the gall bladder, finding no lesions

in the stomach, spleen, kidneys, appendix, lungs or heart. Mentzer et al (41) obtained positive cultures in which streptocci predominated in 98% of their 193 cases when the cultures were made from the wall of the gall bladder.

The importance of biliary stasis in the gall bladder as a factor in the production of cholecystitis has been much discussed but at present the question seems far from being settled.

There is no doubt that stasis of bile in the gall bladder for a long period of time will produce concentration of that bile, but whether this stasis is the cause or the result of cholecystitis has not been definitely proven. The type of individual in which a biliary stasis is most pronounced upon cholecystographic examination, the viscerotonic, is not the type in which biliary disease is most frequent.

The recent work of Aronsohn and Andrews (4) should be mentioned here, for it opens a new field of speculation as to the etiology of gall bladder disease, especially those cases in which few if any bacteria could be demonstrated. Their findings are as follows: after the injection of 6% crystalline pure egg albumen in Ringers solution into the gall bladders of 15 dogs, 13 showed evidence of recent active inflammatory processes in the wall in 48 hours, (edema, fibrinous exudate and hemorrhage). After the dog had been de-sensitized to this material, the result was the same. It is the impression of the authors

that man may give a similar reaction, and that it is in the nature of an anaphylactic condition. They quote Alvarez and Croutch, who had presented cases of gall bladder pain which were caused by chicken, milk, and eggs, as an anaphylactic reaction, and which never recurred after the elimination of these foods from the diet.

The authors also sensitized three dogs to the crystalline egg solution, and then injected the gall bladders as before. The same reaction as before was obtained, but more marked, and occurring in one-half hour after the injection.

Pathogenesis. From a study of the anatomy of the gall bladder it can readily be seen there are four possibilities of a mode of infection of the gall bladder.

1. A descending infection from the liver, the bacteria being carried by the bile.
2. Ascending infections from the duodenum, by way of the common bile duct.
3. Hematogenous or lymphogenous infections.
4. Infection spreading from inflamed contiguous organs.

Of these four possibilities it is only the last two which take into the consideration the actual infection of the gall bladder wall, the first two possibilities assuming contact inflammation through the mucosa. A brief survey of current literature on the bacterial content of bile and of the gall bladder shows a high percentage of sterile bile

cultures. Meyer (44) et al after the intravenous injection of *B. typhosus* (8,000 to 24,000 million) in 500 rabbits found in microscopic evidence of infection of the gall bladder in only one-third of the animals, and they believe that infection of the wall is due to spread from the mucosa, which has been infected by the bile.

Alvarez, et al (2), after making cultures of the walls and bile of gall bladders removed at operation found the wall infected in 63% and the bile in 29%.

Denton (19) in his study of many pathologic gall bladders found a large percentage that were sterile. In 600 necropsies he demonstrated bacteria in 4 out of 94 acute cases. Brown (12) made cultures of various media from 70 gall bladders. His results are tabulated in Table 1. Meyer, Nielson and Feusier (44) state "It is generally known from the studies of Cushing and from our own, that typhoid bacilli introduced directly into the cystic duct of dogs, disappear rapidly, and that cholecystitis can only be produced by considerable injury of the wall, or by placing a foreign body in the gall bladder. (Marzer)"

Graham and Peterman (25) in experiments with 10 dogs in which large amounts of pathogenic colon bacilli were injected into the normal gall bladder found that no cholecystitis was produced sufficient to be demonstrable by gross appearance unless the outflow from the gall bladder was interfered with by ligation of the cystic duct or by injury to the blood supply, produced by ligation of the

cystic artery. One would expect to find a large percentage of cases of cholecystitis in cases of bacteremia if the gall bladder was infected by means of the bile because of the fact that the liver is quite inefficient as a bacteria filter as shown by the experiments shown by Patey and Whitby (52). Osler (51) states that cholecystitis occurred in only 19 of his series of 1500 cases of typhoid fever, a disease in which bacteremia is an almost constant occurrence.

In general there are only two routes available for the transmission of organisms to the wall of the gall bladder. One of these is the blood stream and the other is the lymph stream. A great deal of work has been done in experimental animals in attempting to produce cholecystitis by the intravenous injection of bacteria, and with varying results. Rosenow (57) found that with the intravenous injection of large numbers of *B. coli* and *Strep. viridans* that he was able to produce lesions of the gall bladder tract in 79% of his dogs.

Brown (12) with the intravenous injection of cultures made from tonsillar pus and containing principally *Strep. viridans* produced no lasting bacteremia, no septicemia, and lesions only in the gall bladder. There can be no doubt, apparently, that cholecystitis is not infrequently hematogenous in origin especially with typhoid fever, but in many cases of cholecystitis there is no evidence of a pre-existing bacteremia. If the gall bladder is to be considered as being infected by bacteria coming from other

abdominal organs this infection must arise either as a retrograde thrombus or a pylephlebitis of the cystic vein, which drains into the portal vein.

The most generally accepted evidence on gall bladder infection points to the fact that the cholecystitis represents in a large majority of cases a direct extension to the wall of the gall bladder from a liver which is already infected.

Peterman et al (54) found that in the dog experimental cholecystitis is regularly accompanied by a hepatitis of the same type as found in man. This is most marked in the right lobe of the liver, especially near the gall bladder. If the infection had come to the liver by the portal vein a more even distribution of the hepatitis would be expected. Mann and Willson (37) in 57 cases of acute cholecystitis found associated areas of local chronic inflammatory hepatitis radiating from the gall bladder area. Examination of this microscopically showed connective tissue in the perilobular spaces with subsequent atrophy of the enclosed lobules. Graham (26) showed, in a series of cases in which small pieces of the liver adjoining the gall bladder were removed at operation for cholecystitis, that microscopic evidence of hepatitis existed in every case. Graham together with Peterman (27) found that in a majority of cases, cholecystitis was a direct extension from an already inflamed liver. They found that the hepatitis usually begins and is most marked in the interlobular or periportal spaces, and is apparently due to infection brought to the liver by the

portal vein. They believe that this hepatitis extends to the wall of the gall bladder by means of the lymphatics. Judd (34) agrees with this opinion of Graham's. Patey and Whitby (52) disagree with the work of Graham and believe that the cholecystitis precedes the hepatitis. Reference has been made to the work of Sudler and Kodama who have shown the very intimate lymphatic connection between the liver and the gall bladder. The frequent occurrence of gall bladder infection with disease of the abdominal organs drained by the portal system and particularly the appendix and duodenum has been noted by many authors, among whom are Hargis et al (31), Mann (37), Mayo (30), Graham (28), Davis (17), Constant (15), Walton (65) and Mentzer (43). The latter found that in 80% of his 612 cases of gall bladder disease there was associated disease in the appendix, stomach or duodenum. Graham (25), page 125, performed an experiment which consisted of the production of hepatitis, cholecystitis and choledochitis by portal vein injections. The types of lesion found agreed with those which occur in spontaneous cases in man. It was possible also after the injection for them to demonstrate the infecting organisms in the liver and the wall of the gall bladder. He found that the hepatitis always followed these portal vein injections and it in turn was followed by infections of the gall bladder. He suggests the fact that frequently, perhaps, a vicious circle between the gall bladder and liver is established whereby each may reinfect the other.

Varieties of Cholecystitis. There is nothing specific about the pathological changes in the gall bladder in ordinary inflammation. Acute cholecystitis occurs in many forms. In the simplest of these the organ is reddened, the wall thickened and edematous and the mucous membrane inflamed and congested. Bancroft (6), describing the pathology of this condition, says that the mucosa and villi are relatively normal but there is thickening of the sub-mucosa and muscularis. This condition of acute cholecystitis may pass on to the suppurative stage, empyema of the gall bladder, in which case the organ is greatly swollen and tense and shows black areas if gangrene has set in. The gall bladder in acute cholecystitis usually has patches of cream-colored or yellowish-gray fibrin on its external surface. These may result in the formation of thick, fibrinous adhesions causing the gall bladder to be adherent to adjacent organs. Acute cholecystitis nearly always is caused by obstruction of the cystic duct, usually by stone.

Denton (19) states that the changes in the gall bladder usually due to impaction of stone in the cystic duct, are intramural edema, which is followed by venous distention, and then intramural hemorrhage or hematoma. The amount of damage may range from edema in the submucosa to extensive sub-mucous hemorrhage with destruction of a large amount of the mucosa. However, tags of entirely normal mucosa could be found in the cavity. He found that the intramural edema and hematoma tend to be replaced by scar tissue. He demonstrated bacteria in

the wall in 4 out of 94 acute cases. Upon opening the acute gall bladder, pus and stones are most commonly found. Perforation may result, especially when the infection is due to typhoid bacilli. Microscopic examination of the wall of the gall bladder in cases of acute cholecystitis shows usually the whole wall invaded by leucocytes, and areas of hemorrhage are common. In many cases the deeper layers, especially the sub-serous, are the sites of the most severe inflammatory changes. In the more severe grades the epithelium may be destroyed in places, but it is a striking fact that it rarely if ever is completely destroyed by inflammation. Boyd (10) Miller (45)

Chronic Cholecystitis. Acute inflammation of the gall bladder very often passes into a chronic inflammation, clinical observation showing that a great majority of the gall bladders that become infected remain infected. In chronic cholecystitis the wall is thickened and grayish because of the presence of fibrous tissue. In advanced cases the wall may be a cm. or more thick. There may be many fibrous adhesions to other organs. When the gall bladder is opened the mucosa in some cases will seem to be papilliform but in most cases it will be found to be unusually flattened. The villi are coarsely shaped and often show ulceration of the tips. There is much scar tissue formation, and round cell infiltration of the muscularis. Stones are frequently present. If bile is present it may be either dark and tarry or golden and very thin, closely resembling hepatic bile. This latter

condition probably indicates that the concentrating power has been destroyed by damage to the gall bladder wall Bancroft (6). Microscopic examination shows the wall to be invaded with lymphocytes and plasma cells, many specimens showing polymorphonuclear cells. If calculi are present the cellular infiltration is heaviest just under the mucous membrane. Boyd (10).

Strawberry Gall Bladder. This condition was first described by Moynihan in 1909. (quoted by Graham (28). Boyd (11) has devoted much study to this type of lesion of the gall bladder. He has the opinion that the yellowish material found in the mucosa is an ester of cholesterol. He believes that this substance is normally absorbed from the bile by the gall bladder and that if something interferes with the normal absorption, strawberry gall bladder results. His tabulated results are shown in Table 2. This is also the opinion of Graham (28), Bancroft (6), Denton (19), Mentzer (40) (42). Boyd believes that the most probable factor in preventing the normal absorption is chronic infection, and probably results from the extensive fibrous tissue changes in the wall of the gall bladder.

CHOLELITHIASIS

The incidence of the occurrence of gall stones found in routine post mortem examinations varies considerably. Mentzer (42) in 633 consecutive necropsies at the Mayo Clinic found that 21.67% of adults had stones in the gall bladder. Mayo (39) states that 70% of gall bladder cases have stones.

Stanton (60) found stones in 77% of 282 gall bladder operations. Deaver and Bortz (18) in their series of 903 cases of gall bladder disease found stones in 50%. Cholelithiasis is of much more frequent occurrence in women than in men, the ratio being from 2 to 5 times more frequent. The incidence of gall stones increases as age advances. Mentzer (43) found no stones in persons under 21 in his series of cases, stones occurring most frequently between the ages of 40 and 60.

Walton (65) Rossi (58)

Chemical Constituents.

1. Bile Acids. These usually appear as sodium salts. Gall bladder bile contains from 5 to 10 parts of bile salts, which are of special significance in the formation of gall stones, because they are one of the most important substances in keeping the cholesterol of the bile in solution. Bile salts, if found in stones, are present in minute amounts.

2. Bilirubin and Biliverdin. These are the chief bile pigments. These substances are also held in solution by the bile salts. Bilirubin does not combine readily with the calcium of normal bile, but when the concentration of bile salts becomes low it precipitates out of solution and combines with the calcium to form an insoluble substance, bilirubin calcium.

3. Calcium of the Bile. This substance is secreted in the greater part, by the liver, and, possibly, to some extent by the bile ducts. It is important in that it forms compounds with the bile pigments.

Classification of Biliary Calculi. The usual classification of biliary calculi divides them, essentially, into two types, cholesterol stones and bilirubin calcium stones.

1. Cholesterol Stones. The pure cholesterol stone, containing about 98% cholesterol, is of very infrequent occurrence. It is oval or round in shape, has a crystallin structure and shows no signs of stratification. The laminated stone, which is of slightly more frequent occurrence, contains from 75 to 90% cholesterol and, in addition, small amounts of calcium pigment, these two substances being arranged in alternate layers. By far the most common type of stone is that which is composed of cholesterol and bile pigment. They have no gross crystallin structure, are stratified and have a soft nucleus. They are of various shapes, seldom occur singly, and for this reason are generally faceted.

2. Bilirubin Calcium Stones. These are usually small, ranging from the size of a grain of sand to a pea. They consist chiefly of bilirubin calcium mixed with mucus and rarely contain cholesterol. These stones are frequently of intra-hepatic origin.

3. Rare. Imperfectly crystallized cholesterol stones and stones formed of calcium carbonate are found, but very rarely, in man.

The shape of biliary calculi is subject to great variation. In general it depends on the type of stone, its location in the biliary tract, and the number of stones present. Single stones are round or ovoid, multiple stones are faceted due to pressure and friction upon each other.

There are a number of predisposing causes of biliary calculi. The presence of a nucleus, upon which substances, which crystallize out of the biliary solution can form, is essential. This may be a mass of bile pigment but is usually formed of desquamated cells. Bancroft (6), blood, Denton (19), bacteria, Oliver (50), mucus or precipitated proteins. Biliary stasis also seems to be an essential predisposing condition. Clinical observation shows that sedentary habits, obesity, pregnancy, lack of exercise, and organic obstruction dispose to stagnation of bile in the gall bladder, which favors the multiplication of bacteria, if present, in the bile. The growth of these bacteria, with a resultant change in the reaction of the bile, favors stone formation. Diet seems to play some part in the formation of gall stones. The rate of secretion of bile by the liver, and the emptying of the gall bladder, is influenced by diet. Long intervals between meals and a low fat diet would thus favor stagnation of bile in the gall bladder. Foods which are rich in cholesterol may tend to produce a hypercholesterolemia although this has never been definitely proven. It has been estimated that 80 to 90% of women with gall stones have had one or more children. (19) (58) Mentzer (43) found gall stones in 82% of 110 women who had been pregnant.

Theories of the Formation of Biliary Calculi.

1. Stasis Theory. In addition to what has already been said about the part which stagnation may play in etiology

of gall stones, the work of Whitaker (66) is of interest. He produced stones experimentally by altering the normal mechanism of filling and emptying of the gall bladder so that stasis and over-concentration of bile resulted.

2. Infection Theory. Normal bile, coming from a normal biliary tract, is sterile. However, as we have seen, it is easy for bacteria to enter the biliary tract from the liver. Infection theory was first suggested by Galippe in 1886 and accepted by Naunyn in 1892 (quoted in (25)). Bacteria are found in the gall bladder wall in the majority of cases of gall stones. (19), (50), (43), (57), (28), (65), (62), (47). The presence of bacteria in the wall do not only alter the motility and concentrating activity of the gall bladder (28) but also change the composition of the bile.

3. Cholesterol Theory. The role of cholesterol in the formation of gall stones is still indefinite, although the greater majority of gall stones contain cholesterol. A great deal of work has been done upon the part this substance plays by Moynihan, Boyd, Mentzer and a number of others. Cholesterol is present in a higher concentration in the gall bladder bile than in the hepatic bile. Whether this is a relative increase due to the physiological concentration of the bile or an actual increase, the cholesterol being excreted into the bile from the blood by the gall bladder mucosa, has never been definitely decided.

The strawberry gall bladder, which, as stated previously, is generally believed to be a condition of cholesterol-

osis, is the precursor in a great number of instances of gall stones. A number of men have attempted to show correlation between hypercholesterolemia and an increase in biliary cholesterol, because of the high number of cases of cholesterosis and cholesterol stones found in women who have previously been pregnant, hypercholesterolemia being known to accompany pregnancy. Jones (33) taking the average normal cholesterol in the blood serum as 1.48 gm./1000 cc. found a hypercholesterolemia in all cases in which cholesterol stones were found in operation. Table 4.

The work of Graham (28) as shown in Table 3 shows the definite increase in cholesterol concentration of the bile after sojourn in the gall bladder (as a result of ligation of the cystic duct). These results would tend to show that cholesterol is excreted and not absorbed by the gall bladder mucosa since if it were absorbed one would expect a relative decrease in cholesterol.

THE SYMPTOMS AND CLINICAL DIAGNOSIS OF CHOLELITHIASIS AND CHOLECYSTITIS

Inflammation of the gall bladder shows itself in many forms, the clinical picture, therefore, being varied. Because of the fact that the symptoms and physical findings of many cases of gall bladder stones are similar to those of acute or chronic inflammation of the gall bladder, these conditions will be considered together. Pain is one of the most constant complaints of patients with gall bladder disease, occurring in 96% of Blalock's series (7) of 888 cases, Table 5, with

the next most constant complaints being indigestion, especially for fatty foods, eructation of gas, acid stomach, regurgitation, bloating, constipation, headaches, jaundice, vomiting and loss of weight.

Acute Cholecystitis. Of 848 cases of gall bladder disease at Barnes Hospital, 7.6% were acute cholecystitis. (25) Evidences of peritonitis occur early, causing pain mainly in the upper right quadrant, right rectus rigidity and tenderness, vomiting, leucocytosis and fever. The pain is usually of a continuous, aching character, and may often be cramp-like with severe paroxysms, especially if stones are present. The pain is often referred to the back, especially to the angle of the scapula and the lower dorsal spine. This pain usually subsides in 24 to 48 hours and in 7 to 10 days the acute symptoms are usually gone. Chills, if they occur, are usually not severe and the fever is not, as a rule, high (102°) unless there is a fairly extensive involvement of the liver.

If stones are not present there is usually no jaundice. If jaundice is present it indicates an obstruction of the hepatic bile, due either to stones in the hepatic or common ducts, or to an inflammatory obstruction of the intrahepatic ducts by edema, and cellular infiltration. Leucocytosis is generally from 12 to 18000. Respirations, especially deep respirations, are painful and usually restricted on the right side.

In acute cholecystitis with stone impacted in the cystic duct, nothing flows in or out of the gall bladder, but

the mucous membrane continues secreting mucus as long as possible. The subsequent rapid distention of the gall bladder causes excruciating pain in the upper right quadrant. This pain is paroxysmal and severe, rather than continuous, and ceases abruptly if the stone drops back into the gall bladder or is passed.

Physical examination, aside from upper right rectus rigidity, is rather unsatisfactory. Some enlargement of the liver may be present, and if palpable it is found to be abnormally tender along its entire edge.

Diagnosis is usually easy in the typical case and can be made in most instances by the history. However, almost any other acute intra-abdominal condition may have the same symptoms, especially acute appendicitis or perforated peptic ulcer. The latter may particularly be confusing if the attack of acute cholecystitis is an exacerbation of a chronic cholecystitis which has been giving gastric symptoms, as the history of chronic dyspepsia may be considered that of a peptic ulcer. Postponement of operation because of mistaken diagnosis can be dangerous. The peritonitis resulting from an acute appendicitis or a perforated peptic ulcer is usually more severe than that occurring with acute cholecystitis, the location of maximal tenderness is different, and, in the case of appendicitis, the age of the patient is important. Appendicitis is most frequent in young adults, while cholecystitis is most frequent in middle age, in women, and in the obese. With acute pyelitis and renal colic, pus or blood is found in urine.

Serious cardiac conditions (coronary thrombosis, infarction, or angina) may give symptoms very similar to acute cholecystitis even to tenderness and rigidity in the upper right quadrant. This latter condition is due to the sudden engorgement of the liver with blood. The results of a comparison of the symptoms and physical findings of cholelithiasis and coronary occlusion made by Faulkner et al (23) are tabulated in Tables 6 and 7.

Pneumonia and pleurisy on the right side must also be differentiated, especially diaphragmatic pleurisy. With these two conditions, of course, there are the usual lung findings of a pneumonia process.

CHRONIC CHOLECYSTITIS

Chronic cholecystitis is one of the most frequent ailments of adult humanity. All cases of this condition may not be definitely infectious, i. e., the Strawberry Gall Bladder, which, however, causes symptoms analogous to true chronic cholecystitis. Perhaps a better term for this group of gall bladder diseases would be chronic cholecystopathy.

Chronic cholecystitis is chiefly a disease of middle age, with its origins in early life, probably an attack of acute cholecystitis. This disease has a much higher incidence of occurrence in women than in men, especially in the obese and those who have had multiple pregnancies. A phrase used by many authors to describe the female patient who is most liable to have a chronic inflammatory condition of the gall bladder is "female, fat and forty."

The symptoms of chronic cholecystitis are extremely varied, ranging from recurring attacks of severe biliary colic, which is sometimes followed by jaundice, to vague complaints of "stomach trouble." Those patients who complain of recurrent colic most likely have stones. Graham (25) found that 55% of 380 gall bladders removed at Barnes Hospital with a post-operative diagnosis of chronic cholecystitis, contained stones. Some patients give a history of spells of vague soreness or discomfort in the upper abdomen, a little more marked on the right side. Still others may have only dyspeptic symptoms, or perhaps disturbances in other parts of the body, as the joints, caused by the gall bladder as the focus of infection. Many patients complain of a qualitative food dyspepsia, especially for greases and greasy foods, raw apples, cabbage and other foods of slow digestion; eructations or a constant sensation of gas in the stomach is a very frequent symptom. The gastric symptoms may occur before meals, two to three hours after meals or late at night. Constipation, sometimes extending over several years, may be complained of and many patients have the "laxative habit." The dyspepsia occurring with chronic cholecystitis has never been explained. A number of men have attributed it to an alteration of the gastric secretion but reports on this are not conclusive. Bonar (8) in his series of cases of chronic cholecystitis found that 49% had achlorhydria, 23% had hyperchlorhydria, and 28% had a normal reaction. Griffiths (29) found 90% of his cases to have a hyperchlorhydria. Piersol and Bockus (55) studied the pancreatic enzymes in 40 cases of chronic cholecystitis, and found

them to be diminished in 85% of the cases. Blalock (7) is of the opinion that the dyspepsia is probably due to vague reflex action resulting in disturbed function of the stomach or intestine and leading to eructation, hyperacidity, hypermotility and spastic constipation.

The diagnosis of chronic cholecystitis is difficult because of the variety of symptoms, and hence a painstaking history extending back to the age of 20 must be taken. In a typical history the patient will remember an attack of jaundice or indigestion in the second decade, associated with mild, so-called bilious attacks, headaches, constipation and possibly flatulence. Then develop the "toxemic" symptoms such as periodic headaches with or without nausea, these headaches may resemble migraine; the patient complains that at this time and possibly up until the present he has a practically constant feeling of lassitude; later the patient develops the reflex digestive symptoms of fullness, belching, sour eructation or regurgitation, a foul taste in the mouth and a qualitative dyspepsia. During the third and fourth decades the history becomes more typical. The patient now begins to complain of pain, ranging from severe, sharp, shooting pain in the upper right quadrant to a dull aching sensation in the right hypochondrium, which is referred usually around the bottom of the thoracic cage to the right scapular region. Occasionally the pain may be higher in the shoulder. Swalm (61). Cope (16) states that gall stones and gall bladder disease are less commonly the cause of phrenic shoulder pain than are perforated

pyloric or duodeno ulcer; that neither cholecystitis or stone in the cystic duct caused pain on top of the shoulder unless there is local peritonitis; that stone impacted in the common duct does not cause pain on top of the shoulder until edema and congestion of adjacent parts occurs. Physical examination of chronic cholecystitis is usually uncertain, definite physical signs not being present in all cases. Murphy's sign (the hand is placed deeply under the infracostal margin on the right side, and the patient asked to take a deep breath. As soon as the liver comes downwards on the examining palm an immediate catch in breathing occurs. This should be checked with the opposite side.) is quite suggestive if present. Wolf (69) finds a definite area of tenderness at the tip of the 9th costal cartilage in many cases. He also believes that finding evidences of focal infection such as painful joints or a myocarditis is suggestive. Riesman's ulnar concussion test may be elicited in some cases. In doing this the patient holds a full breath and the examiner alternately strikes the upper right quadrants with the ulnar surface of the hand. This test may cause pain in the upper right quadrant if gall bladder disease is present. Slight enlargement of the liver may be detected and in many cases there is a palpable cecum and a contracted descending colon.

There are a number of fairly common pathological conditions which must be considered in the differential diagnosis of chronic gall bladder disease. The patient with spastic constipation often complains of severe cramping pain in the

right upper quadrant and may even have nausea and vomiting. If tenderness is present it is usually more diffuse than that which occurs in gall bladder disease and extends sometimes over most of the transverse and descending colon.

Intestinal allergy may give symptoms which imitate recurrent attacks of cholecystitis. The physician should be very careful in making his diagnosis, if the patient has hay fever or asthma.

Chronic appendicitis symptoms may closely resemble those of chronic cholecystitis, especially in a high appendix. The definite tenderness in McBurney's point may help to differentiate this condition, however the fact must not be lost sight of that chronic appendicitis is not infrequently associated with chronic cholecystitis.

Various types of cirrhosis of the liver may cause confusion in diagnosis. As the liver pathology increases, of course, ascites and other signs of portal obstruction become evident. Biliary cirrhosis, however, is associated with and probably due to long standing infection of the gall bladder and biliary ducts.

In lesions of the spine, particularly in Potts Disease of the lower thoracic vertebrae, the pain may be referred to the upper right quadrant and there may even be a spasticity of the muscles in this area. However, in this disease there are definite spinal signs such as limited dorsiflexion, pain in the back and spinal weakness.

Intrathoracic inflammatory lesions on the right side, such as chronic pleuritis, may give pain symptoms suggestive of chronic gall bladder disease but the definite history of chest infection plus a careful examination of the thorax will identify this condition.

The most difficult problem in differential diagnosis is that of lesions of the stomach and duodenum, especially chronic peptic ulcer. Unless there is a typical history of food, pain, food, relief, the only way in which this condition may be differentiated is by X-ray examination.

TABLE I

	% showing strep.		B. coli		No growth
Gall bladders showing slight changes	: 30	:	18	:	58
	:	:	:	:	:
Gall bladders showing marked changes	: 75	:	15	:	25
	:	:	:	:	:

TABLE II

Normal gall bladder showed. . .	.0.51-1.70%	cholesterol by weight
Inflamed gall bladder showed. .	.0.36%. . .	cholesterol by weight
Strawberry gall bladder showed.	34.60-60.54%	cholesterol by weight

TABLE III

Increases in cholesterol concentration of the bile after sojourn in the gall bladder (by ligature of the cystic duct).

Dog	Cho. of bile				Concentration of bile as shown by bilirubin content		
	Duration of Experiment	At Operation	At Autopsy	Change	At Operation	At Autopsy	Change
	Days	mgn./cc.	mgn./cc.	%	mgn./cc.	mgn./cc.	%
25	6	0.42	2.71	+520	0.071	0.071	0
A	1	0.50	0.88	+76	0.041	0.50	+22
B	2	0.75	1.45	+93	0.061	0.127	+127
320	14	0.95	1.20	+26	0.92	0.34	-62
324	13	1.15	1.50	+31	1.3	0.70	-46
166	15	0.79			1.4		
WH	7	0.42	0.78	+86	3.33	1.18	-65

TABLE IV

Average normal of cholesterin in blood serum
is 1.48 gm./1000cc.

Case	Cholesterol	
6	5.2	Gallstones at operation
10	3.22	" " "
11	5.55	" " "
12	5.57	" " "
13	9.49	" " "

Hypercholesterinemia persists after operation

15	4.77	3 days post-operative	Stones found.
16	2.13	4 " "	" " "
17	2.10	5 " "	" " "
18	3.77	5 " "	" " "
19	3.36	6 " "	" " "
20	3.96	19 " "	" " "

TABLE V

888 cases, exclusive of neoplasms, at Johns
Hopkins Hospital

Pain	96%
Radiation of pain	51%
Indigestion	86%
Nausea	76%
Vomiting	73%
Constipation	62%
Eructation	59%
Chills and fever	62%
Loss of weight	66%
Jaundice	55%
Itching of skin	13%

TABLE VI

Symptom	Coronary Occlusion	Cholelithiasis
Nausea	5	12
Vomiting	7	16
Palpitation	3	0
Dyspnea	17	0
Syncope	6	0
Faintness	5	0
Vertigo	3	0
Weakness	4	2
Tenderness in r. u. q.	5	23

TABLE VII

Position of Pain	Coronary Occlusion	Cholelithiasis
Precordial	2	0
Substernal	2	0
Chest	1	0
Precord. & Epigastric	2	0
Epigastric	5	15
Lower Abdomen	2	0
Diffuse over abd.	1	0
R. U. Q.	0	9
R. U. Q. & Epigast.	0	1
Lower rt. thorax	0	2
Left breast	0	1
Both flanks	0	1
Angle of Rt. scapula	0	1

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